TOLERANCE REASSESSMENT ELIGIBILITY DOCUMENT FOR Poly-D-Glucosamine (CHITOSAN) 40 CFR 180.1072

A. Background.

Poly-D-glucosamine (chitosan) is a modified natural polymer derived by heating and chemically treating the polysaccharide chitin. Chitin is one of the three most abundant polysaccharides found in nature, along with cellulose and starch. It ranks second only to cellulose as the most plentiful organic compound on earth. It is found in the shells of crustaceans (e.g. crabs (primary source is Dungeness crabs), shrimp, and lobster), in the exoskeleton of marine zooplankton (including coral), in the exoskeleton and wings of insects, and in the cell walls of yeast, mushrooms and other fungi.

Chitin was first described in 1811 by Henri Braconnot, a professor of Natural History and the Director of the Botanical Gardens at the Academy of Sciences in Nancy, France. During the 1830's, chitin was isolated from insect exoskeletons and named. The polymer chitosan was subsequently isolated in 1859 at the Botanical Gardens at the Academy of Sciences in Nancy, France, by C. Rouget. Over the course of the next century, much of the fundamental research took place for chitin and the polymer chitosan. During the 1930s and early 1940s there was an intense interest in new applications for this polymer, as evidenced by the establishment of almost 50 patents. Commercial development was thwarted , however, by the lack of manufacturing facilities and competition from synthetic polymers. A renewed interest in chitosan was sparked in the 1970s by a need to better utilize shellfish shells resulting from food processing. EPA first granted a product registration fo rchitosan in 1986, (Yea! Poly-D-Glucosamine Solution, EPA Registration No. 56437-1), as a plant growth regulator. An exemption from the requirement of a tolerance was initially established for Poly-D-Glucosamine when used as a seed treatment on barley, beans, oats rice and wheat. The exemption from the requirement for a tolerance was broadened for Poly-D-gulcosamine on April 19, 1995 when the active ingredient is used as a plant growth regulator in the production of any raw agricultural commodity.

There are four products registered by EPA that contain the active ingredient, chitosan:

EPA Registration No.	Product Name
56437-1	Yea! Poly-D-Glucosamine Solution
70464-1	ELEXA
70464-3	ELEXA- 4
73882-1	Acrilan Additive - chitosan

No reports of adverse incidents or other problems have been received by the Agency in the period since initial registration of these products.

B. Data Summary

Human Health Assessment

The toxicity information submitted in support of the registration of the technical manufacturing use and end-use products containing the active ingredient Chitosan adequately satisfies the requirements in 40CFR180.1072 for the establishment (reassessment) of the tolerance for a biochemical pesticide. The overall toxicological risk from human exposure to chitosan in these products is considered negligible.

The following data were submitted and reviewed in support of the original tolerance petition and product registration:

Acute Oral Toxicity

For the registration of ELEXA (EPA Registration No. 70464-1), Agency scientists reviewed an acute oral toxicity study in which a limit dose (5000 mg/kg) of the test material (ELEXA - 95% chitosan) was administered by gavage to male and female rats. All treated animals gained weight during the study and no clinical symptoms where observed. The LD_{50} for chitosan was determined to be greater than 5000 mg/kg. Chitosan is classified in Oral Toxicity Category IV.

The Agency also reviewed two feeding studies from published scientific literature that had been submitted in support of the registration for the product, ACRILAN® Additive CHI, (EPA Reg. No. 73882-1). While these studies were conducted to analyze the effects of chitosan on cholesterol, they were determined by the Agency scientists to chitosan be useful in predicting the oral toxicity of chitosan. One study involved feeding 5 rats a 5% diet for 21 days (Jennings, et al., 1988). There were no deaths during the study. In another study, 32 day-old broiler chicks were fed a diet containing 30g/kg of chitosan or other diets for 13 days (Razadan et al., 1997). Mortality for the study was 3%, but this did not appear to be correlated to diet. Based on the findings in these studies, the Agency waived the acute oral toxicity data requirements for this product.

Acute Dermal Toxicity

For the registration of Yea! Poly-D-Glucosamine Solution (EPA Reg. No. 56437-1), a limit dose (2000 mg/kg) application of 95% chitosan was tested on the skin of male and female rabbits. All treated animals gained weight during the study. Slight erythema was observed in 4 males and 2 females at the removal of the coverings, and this cleared by day 2. The LD_{50} was determined to be greater than 2000 mg/kg, and chitosan was classified in dermal Toxicity Category III.

The Agency also reviewed public scientific literature submitted in support of the registration for the product, ACRILAN® Additive CHI, (EPA Reg. No. 73882-1). Chitosan is used in the reconstruction of human skin in burn and wound injuries (Shahabeddin et al: 1990; Damouor, et al:1996; Saintigny, et al: 1993.). Chitosan has also been studied for use as an absorbable suture material (Muzzarelli et.al: 1987). Based on the findings in these studies, the Agency waived the acute dermal toxicity data requirements for this product.

Eye Irritation

After receiving a single (0.5 ml) dose applied to male and female rabbit's eyes, Grade 1 conjuctivitis was seen in 5/6 rabbits (hyperemia) and as well as discharge in 1 of the hyperemic animals at one hour post treatment. This cleared by 24 hours in all animals. Chitosan was placed in Toxicity Category IV (not irritating). Other eye irritation tests, cited in scientific literature, conducted in rabbits following the US Pharmacopeia XXI and Canadian standards, indicated that chitosan was non-irritating (Rao et al: 1997).

Chitosan has been studied for use in contact lens material (Ium, 1998) and has been studied for ophthalmic administration of drugs since it is a biodegradable, biocompatible polymer with bioadhesive properties (Felt et a, 1998; Genta et al: 1997). In these studies up to 2% chitosan was applied to the eye of rabbits 4 times a day for 3 days. No symptoms of irritation, (e.g. conjunctival chemosis and/or redness, discharge or corneal swelling) were seen (Felt et al., 1998). Based on this information, the Agency waived the eye irritation requirements for the registration of Solutia's product, ACRILAN® Additive CHI, (EPA Reg. No. 73882-1).

Acute Inhalation Toxicity

For the registration of ELEXA, a single maximum achievable dose (>3.6 mg/L) concentration of the product was tested in male and female rats. All treated animals gained weight during the study and no clinical signs were observed. Necrospsy findings were unremarkable except for 2 females having dilated uterine horns. The LC_{50} of ELEXA was determined to be greater than 3.6 mg/L. Chitosan is classified in Toxicity Category IV for inhalation.

The Agency granted a waiver to the registrant for the product Solutia, based on particle size and published literature they submitted citing studies using chitosan in nasal drug delivery systems. Chitosan is used as a means of increasing mucosal absorption to prevent rapid clearance of drug delivery systems from the nasal cavity in a number of prescription drugs of drugs (Soane et al., 1999).

Primary Dermal Irritation

A single dose of chitosan (99%) was applied to shaved rabbit skin. No erythema or edema was observed for a period of 72 hours after application. The Agency classified chitosan in Toxicity Category IV for dermal irritation. The Agency waived the primary dermal toxicity data requirements for the product ELEXA, (EPA Reg. No73882-1) based on numerous citations in public literature identifying chitosan treated materials as a wound dressing and skin equivalent in treatment of burns.

Dermal Sensitization

Data submitted for the registration of ELEXA indicated that the test compound (95% chitosan) was not a dermal sensitizer in male Hartley guinea pigs in a modified Buehler method (Ritz and Buehler, 1980).

Subchronic Toxicity

The manufacturers of Chitosan products requested that the Agency waive the Subchronic Toxicity data requirements: Studies to detect genotoxicity; Cellular immune response; 90 Day Feeding Study; and Teratogenicity. The manufacturers based their waiver requests on the low concentrations of chitosan in their products, its low toxicity, and the widespread, natural occurrence of this material in the environment. The Agency granted a waiver for all of these studies. (See review dated August 11, 1997, R. Kumar). However, any incidents of hypersensitivity resulting from the labeled uses of chitosan products must be reported in accordance with 6(a)(2) of FIFRA. If such incidents occur, the immune response studies may be required.

Chronic Toxicity

Chronic exposure studies are conditionally required to support food uses of biochemical pesticides only if the potential for adverse effects are indicated based on (1) the subchronic effect levels established in Tier I subchronic oral, inhalation, or dermal studies (these were waived for the reasons cited above), (2) the pesticide use pattern, or (3) frequency and level of repeated human exposure is expected. Oncogenicity studies are required to support food uses only if the active ingredient or any of its metabolites, degradation products, or impurities produce, in Tier I studies, morphologic effects in any organ that potentially could lead to neoplastic changes. The Agency scientists have determined that the triggers for chronic exposure and oncogenicity testing have not been met and at this time the Agency is not requiring these studies.

C. Search for Recent Information

A web search included Toxline, Google, and other sites. The Toxline search produced one citation related to the toxic effects of poly-d-glucosamine on Powdery Mildew on barley and wheat.

The web search on Google found over 14 citations for poly-d-glucosamine, toxic effects. However, most of these were part of the initial toxicology packages the Agency reviewed as part of the registration and tolerance exemption process for this active ingredient.

D. FQPA Assessment:

1. Infants and Children. Based on the scientific data reviewed, the Agency has determined that chitosan is not likely to pose any hazards to infants and children consuming food treated with these compounds because of low toxicity, lack of toxic endpoints and very low use rates.

2. Validity and Completeness of Data. The Agency's information on chitosan is relatively recent and remain valid to supports the existing tolerance.

3. Nature of Toxic Effects. The toxic effects are very low and do not pose unreasonable health or environmental hazards.

4. Relationship of the Available Information to Human Risk. The information available to the Agency is consistent with the requirements for biochemical pesticides. Chitosan is not expected to pose any human health hazards.

5. Information on Dietary Consumption. Based on the scientific data available to the Agency (e.g., low toxicity, lack of toxic endpoints and very low use rates), the use of these products is not expected to pose dietary risks to humans.

6. Cumulative Effects. The toxicity of chitosan is very low, and there would be no expected cumulative effects from common mechanisms of toxicity.

7. Aggregate Exposure. Aggregate exposure to chitosan-based products would primarily occur with agricultural workers, turf workers, and, to a lesser extent, home gardeners, through dermal, inhalation, and eye irritation routes. Results of the acute oral toxicity (Toxicity Category IV), dermal toxicity (Toxicity Category III), acute inhalation (Toxicity Category IV), primary eye irritation (Toxicity Category IV), and dermal irritation (Toxicity Category IV) indicated low toxicity by these routes of exposure. Based on these results and the lack of toxicity endpoints, the risks from aggregate exposure to chitosan via oral, dermal, eye, and inhalation exposure are a compilation of four low risk exposure scenarios and are considered negligible.

8. Sensitive Subgroups. Because of the low application rates and toxicity of chitosan and the widespread, natural occurrence of the chitosan is material in the environment, the Agency has concluded that risk from the consumption of residues in treated crops is not expected for the general population, including sensitive sub-populations such as nursing mothers, infants and children.

9. Estrogen and Endocrine Effects. EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally-occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific basis for including, as part of the program, the androgen- and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP). When the appropriate screening and or testing protocols being considered under the Agency's Endocrine Disruptor Screening Program have been developed, chitosan may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

Based on the weight of the evidence of available data, no endocrine system related effects have been identified for chitosan.

10. Safety Factor. Since chitosan is ubiquitous, has a very low toxicity and no toxic endpoints, no additional safety factor is required.

E. Conclusion

The existing data and other information used to support the existing tolerance exemption of chitosan (40CFR180.1072) have been re-examined and found to fulfill current Agency standards for this kind of biochemical pesticide.

EPA concludes that the tolerance exemption for chitosan has been reassessed and is in compliance with the FQPA

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